REMARKS

Status of the claims

Claims 1-11 and 15 were previously cancelled. Claims 13-14, 20 and 23-25 stand withdrawn from consideration.

Claims 12, 16-19 and 21-22 stand rejected.

The acceptance of the correction of inventorship is noted with appreciation.

The withdrawal of the prior rejection under 35 U.S.C. 102(e) in view of Bedian et al. (US 2005/00591113) is noted with appreciation.

In the Action of August 31, 2010, the claims were rejected as anticipated by Devalaraja et al. (U.S. 7,108,852, hereinafter "Devalaraja"), as anticipated by Hamilton et al. (U.S. 7,455,836, hereinafter "Hamilton"), and as obvious over Davalaraja and/or Hamilton in view of Buschmann et al. (U.S. 7,507,705, hereinafter "Bushcmann"), Renner et al. (US 2004/0053365, hereinafter "Renner") and page 1, paragraph 3 of the specification herein. Each of these grounds of rejection will be addressed in turn.

In support of this application, Applicants submit herewith the Declaration of Diane Marshall, PhD., under 37 CFR 1.132, with exhibits. Dr. Marshall is a co-inventor of this application, and highly knowledgeable in the area of research of treatments for IBD. Also submitted herewith is an Information Disclosure Statement citing the references that are exhibits to the Marshall Rule 132 declaration.

102 – Devalaraja

Inflammatory bowel disease (IBD) refers to serious, chronic disorders of the intestinal tract characterized by chronic inflammation at various sites in the gastrointestinal tract. Its cause is not known, although genetic and environmental factors are believed to contribute to susceptibility to IBD. Various attempts have been made to provide therapies for those suffering from IBD. Such attempts have included the use of steroids and non-steroidal anti-inflammatory drugs (NSAIDs) such as 5-aminosalicylic acid drugs. Such treatments can be problematic, in that these drugs may not be suitable for long-term use, and are not effective in some 30% of IBD patients. For these patients,

attempted therapies have included immunosuppressive and immunoregulatory agents; in some cases surgery is required. In that regard, many different cytokines and T-lymphocyte cell types have been implicated in IBD, all of which present potential targets for IBD treatment. (Marshall Decl. ¶ 4)

Thus it is recognized in the art that IBD and its treatment are both unpredictable. It cannot be known which proposed treatments will be effective for particular patients. In particular, not all anti-inflammatories are effective in the treatment of IBD. Steroids and NSAIDS, although standard anti-inflammatories for a wide variety of inflammatory disorders, are not effective against IBD for a significant number of patients. Thus, the mere fact that a particular drug is an anti-inflammatory does not mean that it will be effective against IBD, even though IBD is an inflammatory disorder. For some patients, no known treatments are effective. As of the filing date of this application, there is no known cure for IBD. (Marshall Decl. ¶ 5)

Colony stimulating factor 1 (hereinafter CSF-1), also known as macrophage colony stimulating factor (M-CSF) is a cytokine produced by a variety of cells, including macrophages, endothelial cells, and fibroblasts. While many different cytokines and T-lymphocyte cells have been implicated in IBD, it is not known if CSF-1 plays any role in the pathogenesis of IBD, although increased CSF-1 serum levels have been observed in patients with active IBD. (Marshall Decl. ¶ 6)

Devalaraja is directed to methods of treating inflammation using anti-CSF antibodies. Devalaraja states that the invention disclosed therein is connected to the discovery that CSFs appear to be critical for leukocyte recruitment, specifically polymorpho-nuclear neutrophil (PMN) and monocyte recruitment, and exhibit synergizing activity with chemokines (col. 4, lines 3-7). The CSF can be either M-CSF (col. 4, lines 38-39, 62-63), G-CSF (col. 5, lines 16-17, 40-41), or GM-CSF (col. 5, line 60). Devalaraja states that the diseases or disorders treated can include inflammation, osteoporosis, autoimmune disease, and atherosclerosis (col. 6, lines 1-8). Diseases specifically noted are atherosclerosis (col. 6, line 16), sepsis (col. 6, line 25), asthma (col.

6, line 33), autoimmune disease (col. 6, lines 41-42), osteoporosis (col. 6, line 51), rheumatoid arthritis (col. 6, lines 60-61), and osteoarthritis (col. 7, line 3).

In the definition of "autoimmune disease" at col. 11 lines 4-16, IBD is not listed as either "highly probable" or "probable." IBD is not included as one of the "preferred inflammatory diseases" listed at col. 11, lines 21-25. The claims of Devalaraja are limited to a method of treating rheumatoid arthritis, and do not recite any method of treating of IBD.

The data presented in Devalaraja include experiments conducted to confirm that G-CSF synergizes the IL-8 induced chemotaxis in vivo and in vitro (col. 18, line 38 – col., 19, line 17; Figs. 1-13) and experiments conducted to demonstrate that M-CSF synergized MCP-1 induced chemotaxis (col. 19, lines 18-62; Figs. 14-21). Of these, the data related directly to M-CSF is presented at Figs. 19-21. Devalaraja does not include any animal model data for IBD, nor does it contain any animal model data for any of the diseases stated to be treatable by the method disclosed therein.

The statement at page 3 of the Action that

> "As noted previously, the *preferred* use of inhibitors of CSF, including antibody directed to CSF (e.g., col. 4, paragraphs 1-5) described by the prior art teaching [Devalaraja] *is the treatment of IBD* (e.g., see column 7, paragraph 1)." (emphasis added)

is respectfully traversed. The statement in the Action suggests that Devalaraja teaches that treatment of IBD is the preferred use of anti-M-CSF antibodies, but that is not the teaching of the reference.

The full text of the portion of Devalaraja alluded to in the Action states,

> "The preferred use of the inhibitors of the present invention is for, but not limited to, the treatment of atherosclerosis, osteoporosis, and chronic and acute inflammatory and autoimmune diseases such as SLE, GVHD, RA, IBD, asthma, and psoriasis." (col. 7, lines 4-8)

Devalaraja discusses three types of CSF's, i.e., G-CSF, M-CSF, and GM-CSF, all of which have different properties, and which may not always be substituted one for another, (Marshall Decl. ¶7). In the quoted statement there is no way of knowing which of the three CSF's or their antibodies is being referred to. Further, Devalaraja at that point lists several diseases, of which autoimmune disease is but one type, with IBD being one of six autoimmune diseases listed. The paragraph thus does not state that treatment of IBD is particularly preferred, or that antibodies to M-CSF are particularly preferred out of the various inhibitors disclosed in the reference.

Devalaraja does not disclose to one skilled in the art a treatment of IBD by administration of anti-M-CSF antibodies (Marshall Decl. ¶14). IBD is not included in the list of individual diseases at column 6, nor is it explicitly included in the definition of "autoimmune disease" at col. 11, lines 4-16, and a method of treating IBD is not recited in the claims. The only time IBD is mentioned is at col. 7, lines 4-8, but that statement is with respect to "preferred use of inhibitors of the present invention" and does not specifically mention anti-M-CSF antibodies. The patent does not limit such "inhibitors" to anti-M-CSF antibodies, but also includes data for anti-G-CSF antibodies and anti-GM-CSF antibodies as inhibitors. One skilled in the art would not understand from the sentence at col. 7, lines 4-8 which antibodies Devalaraja intended to suggest for the treatment of IBD. (Id.) Also, the absence of any experiments using an animal model for IBD indicates to the skilled person that Devalaraja did not demonstrate that anti-M-CSF can be effective in the treatment of IBD. (Id.) Given the well-known lack of predictability of the effectiveness of IBD treatments and the fact that not all anti-inflammatory treatments are effective against IBD, the paucity of discussion of IBD in the Devalaraja disclosure suggests to one skilled in the art that Devalaraja was not in possession of a method of treating IBD using an anti-M-CSF antibody or antibody fragment. (Id.) One skilled in the art would not have combined the teachings of Devalaraja with his or her own knowledge to understand that IBD could be treated by the administration of anti-M-CSF antibodies (Marshall Decl. ¶14).

The case law cited in the action does not compel a finding of anticipation. In *Ex parte A*, 17 USPQ2d 1716 (BPAI 1990) claims to a compound were held to be anticipated by a reference which indisputably named a compound that corresponded to the claimed formula and recited and disclosed enabling synthetic procedures. Another claim which broadly recited compounds as "an anti-bacterial composition" was anticipated by a reference which describes forty-six compounds as having "antibacterial activity" and as being "meant for use as active compounds in medicaments." This case is relied upon in the Action for the proposition that "[w]hen the species is clearly named, the species claim is anticipated no matter how many other species are additionally named." But unlike *Ex parte A*, the applicant here is not claiming a compound. The claims here relate to a method of treatment of IBD, a condition which is notoriously unpredictable and difficult to treat. Further, unlike the situation in *Ex parte A*, more is required for enablement of a method of treatment claim than for a compound claim. In the present case, the cited reference merely suggests that some anti-CSF antibodies may be useful against some inflammatory diseases, it does not identify which type of anti-CSF antibodies would be most useful with respect to IBD, and provides no animal model data. Unlike the case of *Ex parte A*, the Devalaraja reference does not provide an enabling disclosure of the presently claimed invention so as to establish anticipation, as evidenced by the Marshall Declaration submitted herewith. Accordingly it is respectfully requested that this ground of rejection be withdrawn.

102 – Hamilton

The rejection of the pending claims as anticipated by Hamilton is respectfully traversed. Like Devalaraja, Hamilton generally suggests the use of inhibitors of CSFs in the amelioration of inflammation in a subject (col. 2, lines 3-9). Targets of the inhibitors can include GM-CSF, M-CSF, and u-PA. Hamilton describes animal studies in which the modeled diseases are asthma, COPD, exacerbation of asthma, and collagen-induced arthritis.

The Hamilton reference is not sufficient to teach one skilled in the art that Hamilton was in possession of a method of treating IBD by administering anti-M-CSF

antibodies. (Marshall Decl. ¶ 15) Hamilton generally discusses treatment of an inflammatory condition by reducing levels of inflammatory and pro-inflammatory mediators such an M-CSF, GM-CSF, IL-1, TNF-α, IL-6, products of COX-s, u-PA and other molecules (col. 5, lines 54-62). The only data presented for anti-M-CSF antibodies is at Figure 2C, and relates to the treatment of collagen-induced-arthritis (CIA). The only animal models presented are for CIA, asthma, and COPD. The claims are limited to the use of anti-GM-CSF antibodies. The statement at column 5, lines 44-50 that "inflammatory condition" relates to chronic inflammation conditions such as rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, type I diabetes, multiple sclerosis, psoriasis and chronic inflammatory lung disease such as asthma, chronic bronchitis, emphysema or chronic obstructive airway disease does not suggest to one skilled in the art that Hamilton was in possession of a method of treatment of either inflammatory bowel disease or Crohn's disease, given the unpredictable nature of these disorders and methods of treatments thereof (Marshall Decl. ¶15).

The fact that anti-M-CSF antibody was shown to have some effect in animal models in the treatment of collagen-induced-arthritis teaches nothing to one skilled in the art about possible treatments for IBD. (Marshall Decl. ¶ 15) Similarly, the data relating to anti-GM-CSF antibodies does not teach one of skill in the art about the effects of anti-M-CSF antibodies, either on the disorders for which anti-GM-CSF antibodies were used, or for any other disorders. (Id.) Nor would one skilled in the art have combined the teachings of Hamilton with his or her own knowledge to understand that IBD could be treated by the administration of anti-M-CSF antibodies. (Id.)

The case *Ex parte A* is inapposite here for the same reasons as stated with respect to the Devalaraja reference.

The Hamilton reference does not provide an enabling disclosure of the presently claimed invention so as to establish anticipation, as evidenced by the Marshall Declaration submitted herewith. Accordingly it is respectfully requested that this ground of rejection be withdrawn.

103 - Devalaraja and/or Hamilton in view of Bushcmann, Renner, and the specification

This ground of rejection is likewise respectfully traversed.

The Devalaraja and Hamilton references have been discussed above.

Renner relates to humanized GM-CSF antibodies. This disclosure teaches one skilled in the art nothing about the properties or effects of anti-M-CSF antibodies. (Marshall Decl. ¶16) Renner discloses at paragraph [0004] that GM-CSF is known to play a role in the development of rheumatoid arthritis. This teaches one skilled in the art nothing about what factors may play a role in the development of other inflammatory diseases. (Id.) Paragraph [0040] recites "inflammatory conditions" including both specific and non-specific immune reaction to an antigen. The fact that IBD is included in this list does not teach one skilled in the art that anti-GM-CSF antibodies would be effective in the treatment of IBD, and even if that were the teaching, it does not teach anything about the effect of anti-M-CSF antibodies in the treatment of IBD. (Id.) Renner does not claim a method for treatment of IBD, or a method of treatment of any disorder.

Buschmann is directed to the use of colony stimulating factor (CSF) or a nucleic acid molecule encoding CSF for preparation of a pharmaceutical composition for enhancing neovascularization and/or the growth of collateral arteries and/or other arteries from preexisting arteriolar connections (col. 5, lines 5-10), and to the use of anti-CSF agents for the suppression of neovascularization or collateral artery growth to treat tumors (col. 8, line 66 – col. 9, line 4). Bushcmann has nothing to do with inflammatory disorders, or the treatment of inflammatory disorders. (Marshall Decl. ¶17) This disclosure does not teach one skilled in the art that these different CSF's or their antibodies are equivalent with respect to the treatment of any inflammatory disease, and does not teach anything about treatment of IBD. (Marshall Decl. ¶17)

In this case, there is no reason to combine Devalaraja with Hamilton, nor would such a conclusion lead one skilled in the art to use anti-M-CSF antibodies in the

treatment of IBD (Marshall Decl. ¶18). The biological and pharmaceutical arts are generally unpredictable, and IBD is notoriously difficult to treat (id.). Devalaraja discusses many other diseases that allegedly can be treated by specific types of anti-CSF antibodies, but mentions IBD only once, and then only as a suggestion of disorders that might be treated, and without specifying the particular type of anti-CSF antibody to be used. Hamilton likewise focuses on other diseases and includes animal models for other diseases, not IBD. The combination of these references would not have led one skilled in the art to believe that the use of anti-M-CSF antibodies in the treatment of IBD would have had a reasonable chance of success (Marshall Decl. ¶18). Renner's teaches the use of anti-GM-CSF antibodies, which if anything teaches away from the use of anti-M-CSF antibodies. Buschmann teaches nothing about inflammatory disease, so there would be no reason why one skilled in the art would combine Bushcmann with the other references, nor would doing so have led one to the presently claimed invention. The fact these references have been available for many years, and yet no one prior to the present inventors have demonstrated the effectiveness of anti-M-CSF antibodies in the treatment of IBD, combined with the long-felt need for an effective method for treatment of IBD, supports the non-obviousness of the claimed invention (id.).

Further, the data presented in the application demonstrates the unexpected results achieved with the presently claimed method, which further supports the non-obviousness of the invention, *Crocs, Inc. v. U.S. Int'l. Trade Comm'n.*, 598 F.3d 1294 (Fed. Cir. 2010).

CONCLUSION

In view of the foregoing, and the evidence presented herein in the form of the Marshall Declaration, it is respectfully requested that the rejection for obviousness be withdrawn, and that the application be passed to allowance.

The Applicants invite the Examiner to contact the Applicants' undersigned representative at (312) 913-3362 if the Examiner believes that this would expedite prosecution of this application.

Respectfully submitted,

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